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Are neutrophil to lymphocyte ratio and platelet to lymphocyte ratio clinically useful for the prediction of early pregnancy loss?

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ABSTRACT

Objectives: Red cell distribution width (RDW), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have all been identified as systemic inflammatory markers. The aim of this study to investigate whether the use of systemic inflammatory markers can predict early pregnancy loss.

Material and methods: A total of 137 patients with early pregnancy loss was compared with 148 participants in the control group who had given birth at term. In the study group, CBC values were included in the study at the time of referral to the hospital for routine follow-up, while patients did not experience early pregnancy loss. In the control group, CBC values of the patient before the seventh week of pregnancy were included in the study.

Results: There was no significant difference between the two groups in terms of RDW, MPV, PCT and PDW values. The NLR and PLR values were significantly higher in the early pregnancy loss group than the control group ($p < 0.05$).

Conclusion: Our findings suggest that high NLR and PLR values are potent markers for the prediction of early pregnancy loss.

Key words: early pregnancy loss; systemic inflammation; inflammatory markers

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INTRODUCTİON

Early pregnancy loss is described as a nonviable, intrauterine gestation with either an empty gestational sac or an embryo/fetus without heartbeat within the first 12 6/7 weeks of gestation [1]. Approximately 10% of all clinically recognized pregnancies ending in an early loss and about 80% of all pregnancy losses occur in the first trimester [1]. Despite the high frequency of early pregnancy loss, its pathophysiology is still not fully understood [2]. Also, the natural history of early pregnancy loss, including temporal ordering of signs and symptoms in early pregnancy has not to be fully described [3]. The causes of early pregnancy losses have been reported in the literature as genetic causes, infectious causes, immunological causes, implantation abnormalities, anatomic abnormalities and endocrine disorders [4]. However, approximately 40% of early pregnancy losses are categorized as idiopathic [4].

Human pregnancy can be defined as the implantation of the semi-allogeneic fetus into the endometrium [5]. Complicated pregnancies such as hyperemesis gravidarum, preterm delivery, preeclampsia, gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, frequently have an excessive inflammatory response that leads to adverse pregnancy outcomes [6]. The role of systemic inflammatory reactions in the pathogenesis of early pregnancy loss has been examined in several studies. In one study, it was stated that the women with euploid miscarriage had significantly higher levels of TNFα, IFNγ, IL-6 and IL-10 compared to normal pregnant controls [7]. However, the technical difficulties and high cost of evaluating inflammatory markers in the blood sample limited the use of these investigations in clinical practice. Parameters such as red cell distribution width (RDW), platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT), platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR), which are readily available as systemic inflammation markers from complete blood count (CBC), are widely used in the diagnosis of many inflammatory diseases and prediction of the complicated pregnancies [8, 9]. The objective of this study to investigate whether the use of systemic inflammatory markers can predict early pregnancy loss.

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MATERIAL AND METHODS

This retrospective study was conducted at the Obstetrics and Gynecology Department of the Gazi Yaşargil Training and Research Hospital, during the period from September 2019 to December 2019. The study was approved by the same hospitals Ethics Committee.

The inclusion criteria of the study group were early pregnancy loss patients with ageing between 18–35 years old. The inclusion criteria of the control group were pregnant women with live birth ≥ 37 weeks and ageing between 18–35 years old. The two groups were matched for age and body mass index (BMI). The exclusion criteria for participation in the study were as follows: women with inadequate data, multiple gestation, molar pregnancy, a history of recurrent miscarriages or infertility, a known thrombophilia or any other medical condition needing chronic drug treatment, complicated pregnancies (preeclampsia, gestational diabetes mellitus, intrahepatic cholestasis of pregnancy), any congenital uterine anomaly, large uterine fibroids and smoking during pregnancy.

Age, gestational week, gravida, parity, body weight and height were obtained by examining the medical records of patients. The gestational week was determined by sonographic measurement. BMI was calculated by dividing the body weight (in kilograms) by the square of the height (m^2).

In the study group, CBC values were included in the study at the time of referral to the hospital for routine follow-up, while patients did not experience early pregnancy loss. In the control group, CBC values of the patient before the seventh week of pregnancy were included in the study. The CBC values of the patients were measured with Mindray BC 6800, an automatic blood counting device using laser and impedance measurement technique. Haemoglobin (Hb), white blood cell count (WBC), neutrophil count, lymphocyte count, platelet (PLT) count, RDW, PDW, MPV, PCT and CRP values were all derived from patient' medical files. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. The PLR was calculated by dividing the platelet count by the lymphocyte count.

Statistical analysis

IBM SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical package program was used for statistical evaluation of our research data. Measured variables were presented as mean±standard deviation (std), and categorical variables were presented as numbers and percentages (%). Kolmogorov-Smirnov test was used to determine whether the numerical data matched the normality distribution. Student's t-test was used to compare the normally distributed data. Mann-Whitney U test was used to compare the non-normally distributed data. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 137 patients with early pregnancy loss was compared with 148 participants in the control group who had given birth at term. The demographic and clinical features of all patients are summarized in Table 1. The median age of the study group was 23, and the median age of the control group was 26. There was no significant difference between the two groups in terms of age, BMI, gravida and parity.

The laboratory values of the groups are shown in Table 2. The haemoglobin, RDW, WBC, PLT count, PCT, MPV, and PDW

Table 1. Demographic and clinical features of the groups

Variables	Early pregnancy loss group (n = 137)	Control group (n = 148)	p value
Age (years)*	23 (18–35)	26 (19–35)	> 0.05
BMI (kg/m^2)**	23.12 ± 3.66	23.78 ± 3.82	> 0.05
Gravida*	3 (1–5)	4 (1–6)	> 0.05
Parity*	1 (0–4)	1 (0–5)	> 0.05

* — median (minimum-maksimum); ** — mean ± standart deviation

Table 2. Laboratory values of the groups

Variables	Early pregnancy loss group (n = 137)	Control group (n = 148)	p value
Haemoglobin (g/dL)*	11.8 (8.6–13.1)	11.4 (9.3–12.7)	> 0.05
RDW (%)**	11.6 ± 1.3	12.2 ± 1.5	> 0.05
WBC (/mm^3 ×10^3)**	9.2 ± 2.6	8.4 ± 2.2	> 0.05
NEU (×10^3/uL)**	4.6 ± 1.4	3.4 ± 1.3	**< 0.05**
LYM (×10^3/uL)*	1.6 (0.4–3.4)	2.3 (0.9–4.2)	**< 0.05**
Platelet (/mm^3 ×10^3)*	264.1 (142.0–431.0)	257.8 (168.0–418.0)	> 0.05
PCT (%)*	0.19 (0.12–0.35)	0.18 (0.13–0.33)	> 0.05
MPV (fL)*	8.8 (6.8–10.9)	8.6 (6.7–10.7)	> 0.05
PDW (%)*	15.8 (15.2–17.4)	15.2 (12.1–16.7)	> 0.05
NLR*	3.5 (1.3–7.1)	1.9 (1.1–4.2)	**< 0.05**
PLR*	150.7 (71.6–339.2)	84.1 (46.4–204.3)	**< 0.05**

* — median (minimum-maksimum); ** — mean ± standart deviation

values were not significantly different between the early pregnancy loss and control groups. The neutrophil count was significantly higher ($p < 0.05$) and the lymphocyte count was significantly lower ($p < 0.05$) in the early pregnancy loss group than the control group. The NLR and PLR values were significantly higher in the early pregnancy loss group than the control group ($p < 0.05$).

DISCUSSION

In this retrospective study, we compared first-trimester systemic inflammatory markers of pregnant women with a live birth at ≥ 37 weeks with those pregnancies ended with an early loss. Our findings indicate that early pregnancy loss has an association with systemic inflammation.

During pregnancy, there is an increase in systemic inflammation [10]. Regulated inflammation is essential in every stage of pregnancy [11]. Physiologic regulation of immune response prevents the rejection of semi-allogeneic fetus, and this regulation is mainly through changes in cytokine levels [10]. Deregulation of this mechanism can cause adverse pregnancy outcomes such as spontaneous or recurrent abortion, preeclampsia, preterm labour, and intrauterine growth restriction [10].

In several studies, it was reported that the cytokine levels are different in women with recurrent miscarriages. In the study of O'Hern Perfetto et al. [12], it was suggested that the lower levels of IL-22 in the uterine decidua in patients with unexplained recurrent pregnancy loss. However, there are conflicting results in the literature about the status of the systemic inflammatory response in spontaneous miscarriage. In a study conducted by Sacerdoti et al. [13], decrease in local vascular endothelial growth factor (VEGF) may contribute to the early pregnancy loss. In contrast, in the study of Ku et al. [14], it was reported that there was no correlation between circulating IL-6 levels with spontaneous miscarriage.

Inflammatory markers, which are associated with early pregnancy loss in various studies, are not available in all centers due to technical difficulties and high costs. The diagnostic value of systemic inflammatory markers such as NLR, PLR, PDW, MPV, PCT, RDW in many diseases such as preeclampsia, coronary artery disease, autoimmune diseases, inflammatory diseases has already been shown in several studies [15, 16]. However, there are few studies and insufficient data in the literature on the relationship between these markers and early pregnancy loss. In this study, we planned our study to evaluate whether these markers, which we can quickly obtain with the complete blood count, have changed in patients before early pregnancy loss.

High RDW values are thought to reflect increased inflammation and oxidative stress [17]. In addition to their central role in hemostasis, studies have shown that platelets are potent immune modulators and effectors [18]. PDW, MPV and PCT are regarded to be markers of platelet activation [19]. It was shown that PLT count, PCT and RDW was significantly higher in patients with recurrent pregnancy loss than in controls [20]. However, in our study, there was no significant difference between the early pregnancy loss and control groups in terms of RDW, PLT count, PCT and MPV values. These results suggest that platelet activation may not have a significant role in the pathogenesis of inflammation in spontaneous early pregnancy loss. These results can also be explained by the exclusion of patients with recurrent abortion or chronic diseases into the study. Studies with a large number of patients needed in this regard.

In many systemic inflammatory diseases and malignancies, the physiological response of the immune system is to increase the neutrophil count and decrease in lymphocyte count, and this has lead to the widespread use of NLR and PLR values in the diagnosis and evaluating the prognosis of inflammatory diseases [21]. Also, in several studies, it was reported that high NLR values during the first trimester were powerful predictors of subsequent complicated pregnancies such as preeclampsia, gestational diabetes and intrahepatic cholestasis of pregnancy [22–24]. However, there are few studies investigating the association between NLR and PLR values and early pregnancy loss. In a study by Christoforaki et al., it was found that NLR does not differ significantly between pregnant women with live birth and those whose pregnancy ended in miscarriage [25]. In contrast, in the study of Bas et al., NLR and PLR values evaluated at the sixth gestational week can be used for the risk assessment of spontaneous abortion. In our study, when the groups were compared, NLR and PLR values were significantly higher in the early pregnancy loss group than the control group.

The strength of the study is that there are few studies in the literature about predicting early pregnancy loss with systemic inflammatory markers. Excluding women with all possible confounding factors that can cause early pregnancy loss, such as advanced maternal age, multiple pregnancies, recurrent miscarriage, chronic diseases is another strength of the study.

There are some limitations to this study. This study has been designed retrospectively and has the potential to contain limitations of such studies. Another limitation is the absence of pro-inflammatory cytokines such as TNF-α, VEGF, IL-6, which have been previously identified with early pregnancy loss. A study by correlating the results of systemic inflammatory markers with these cytokines may provide more insight into the prediction of early pregnancy loss.

CONCLUSİON

The results of this study suggest that NLR and PLR are potent markers in the prediction of early pregnancy loss.

Conflict of interest

The authors declared no conflict of interest.

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